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M99/0035/GB

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-5 FEB 1999

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

NEUTEC PHARMA PLC
St James's Court
Brown Street
Manchester
M2 2JF

Patents ADP number *(if you know it)*

GB

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7391071001

4. Title of the invention

Medicament

5. Name of your agent *(If you have one)*

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

McNeight & Lawrence
Regent House, Heaton Lane
Stockport, Cheshire SK4 1BS

Patents ADP number *(if you know it)*

0001115001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

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Number of earlier application	Date of filing *(day / month / year)*

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Continuation sheets of this form	
Description	21
Claim(s)	03
Abstract	
Drawing(s)	

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Request for preliminary examination and search *(Patents Form 9/77)*	
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11. I/We request the grant of a patent on the basis of this application.

Signature McNeight & Lawrence Date 05/02/99

12. Name and daytime telephone number of person to contact in the United Kingdom James A Robertson 0161-480-6394

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Medicament

The present invention concerns treatment, prevention and diagnosis of infection due to *Chlamydia pneumoniae* and in particular to the prevention and treatment of atherosclerosis, including coronary atherosclerosis, caused by same.

C. pneumoniae is associated with atherosclerosis but no definitive link between the two has yet been established (Hammerschlag, M.R., 1998, Eur. J. Clin. Microbiol. Infect. Dis., 17: 305-308). Friedank, H.M. *et al.* (1993, Eur. J. Clin. Microbiol. Infect. Dis., 12(12): 947-951) identify a 54 kDa *C. pneumoniae* antigen which was recognised by 93% of sera positive for *C. pneumoniae*, the antigen appearing to be located on the surface of elementary bodies. Wiedman, A.A.M. *et al.* (1997, Clin. Diagn. Labs. Immunol., 4(6):700-704) showed the infectivity of *C. pneumoniae* elementary bodies to be slightly reduced by the use of antibody specific against a 54 kDa *C. pneumoniae* protein.

Other researchers have not identified an immunogenic *C. pneumoniae* 54 kDa band (see for example Kutlin, A. and Roblin, P.M., 1998, J. Infect. Dis., 177: 720-724; Campbell, L.A. *et al.*, 1990, J. Clin. Microbiol., 28(6): 1261-1264; Campbell, L.A. *et al.*, 1990. Infection and Immunity, 58(1): 93-97; Puolakkainen, M. *et al.*, 1993, J. Clin. Microbiol., 31(8): 2212-2214; hkima, Y. *et al.*, 1994, J. Clin. Microbiol., 32(3): 583-588; Maass, M. and Gieffers, J., 1997, J. Infection, 35: 171-176; Gonen, R. *et al.*, 1993, APMIS, 101:719-726).

The present inventor has now succeeded in isolating, purifying and identifying *a C. pneumoniae* protein which (together with inhibitors of same, such as

antibodies) is protective and therapeutic against *C. pneumoniae* infection. The therapeutic role of the protein has previously neither been suggested nor disclosed.

According to the present invention there is provided a *C. pneumoniae* protein having the amino acid sequence of SEQ ID NO: 2, for use in a method of treatment or diagnosis of the human or animal body. The amino acid sequence has been confirmed by N-terminal amino-acid sequencing (see "Experimental" below) and the protein has a theoretical molecular weight of 50.8 kDa, although post-translational modifications such as glycosylation may of course affect its apparent molecular weight as determined by e.g. SDS-PAGE. Experiments (below) have shown it to have an apparent molecular weight of 51 kDa on SDS-PAGE gels.

As can be seen from the plethora of publications above, although some identify immunogenic bands at molecular weights of 50-54 kDa, no specific therapeutically effective proteins have been identified.

Experiments (below) have allowed the present inventor to isolate and purify the protein of the present invention and identify the gene sequence coding for the protein. This has allowed the determination of the protein amino acid sequence (above). The nucleotide sequence coding for same forms another part of the present invention. Thus according to the present invention there is also provided a nucleotide sequence coding for a protein according to the present invention, for use in a method of treatment or diagnosis of the human or animal body. Such a nucleotide sequence may have the sequence of SEQ ID NO: 1. Modified nucleotide sequences having codons encoding the same amino acid sequence will be readily apparent to one skilled in the art.

The nucleotide sequence of the present invention and the amino acid sequence it encodes are already known from the Chlamydia Genome Project

(*C. pneumoniae* CWL029/CPn0809), as is an apparent *C. trachomatis* homologue (CT578). However, therapeutic and diagnostic uses for same have not been previously suggested.

The invention also extends to encompass forms of the protein which have been insubstantially modified (i.e. which have been partially modified), particularly forms of the protein which display the same immunogenic properties as the protein itself.

By "partial modification" and "partially modified" is meant, with reference to amino acid sequences, a partially modified form of the molecule which retains substantially the properties of the molecule from which it is derived, although it may of course have additional functionality. Partial modification may, for example, be by way of addition, deletion or substitution of amino acid residues. Substitutions may be conserved substitutions. Hence the partially modified molecule may be a homologue of the molecules from which it was derived. It may, for example, have at least 70% homology with the molecule from which it was derived. It may for example have at least 80, 90 or 95% homology with the molecule from which it was derived. An example of a homologue is an allelic mutant.

Also provided according to the present invention is the use of a protein, immunogenic fragment thereof or nucleic acid sequence encoding same according to the present invention in the manufacture of a medicament for the treatment of infection due to *C. pneumoniae*.

Immunogenic fragments of the protein include any fragment of the protein which elicits an immune response, and includes epitopes. Similarly, analogues (mimotopes) of epitopes may be readily created, the mimotopes having different sequences but displaying the same epitope and thus the term "immunogenic fragments"

also encompasses immunogenic analogues of the fragments e.g. mimotopes. Epitopes may be readily determined and mimotopes readily designed (Geysen, H.M. *et al.*, 1987, Journal of Immunological Methods, 102: 259-274; Geysen, H.M. *et al.*, 1988, J. Mol. Recognit., 1(1):32-41; Jung, G. and Beck-Sickinger, A.G., 1992, Angew. Chem. Int. Ed. Eng., 31: 367-486). Such an immunogenic fragment carrying epitopes may also be described as being a peptide having the amino acid sequence of the immunogenic frament and which carries an epitope.

The present inventor has succeeded in isolating a number of epitopes (immunogenic fragments) of the protein of the present invention. Thus according to the present invention there is also provided an epitope having the amino acid sequence of any one of SEQ ID NOs: 3-11.

The protein, immunogenic fragments thereof and nucleic acid sequences encoding same may be used in therapy, both prophylactically (e.g. as immunostimulants such as vaccines) and for treatment of infection due to *C. pneumoniae*. For example a nucleotide sequence encoding the protein or immunogenic fragment thereof may be used in the manufacture of a DNA vaccine (Montgomery, D.L. *et al.*, 1997, Pharmacol. Ther., 74(2): 195-205; Donnelly, J.J. *et al.*, 1997, Annu. Rev. Immunol., 15: 617-648; Manickan, E. *et al.*, 1997, Crit. Rev. Immunol., 17(2): 139-154)

Binding agents and inhibitors (such as antibodies or other neutralising agents) specific against the protein and immunogenic fragments thereof may also be used both diagnostically and therapeutically. Binding agents have a target to which they are specific, and in the case of a binding agent being an antibody, the target is an antigen. An example of a therapeutic medicament is antibody specific against the protein of the present invention, and this may be employed in immunotherapy, for example passive immunotherapy. Antibodies, their manufacture and use are well known (Harlow, E. and

Lane, D., "Using Antibodies - A Laboratory Manual", Cold Spring Harbor Laboratory Press, New York, 1998) and so antibodies and antigen binding fragments thereof will be readily apparent to one skilled in the art, and reference herein to antibodies is also reference to antigen binding fragments Other inhibitors such as ribozymes, antisense oligonucleotides and DNA vaccines will be readily apparent to one skilled in the art.

Thus the present invention also provides the use of a inhibitor specific to the protein of the present invention in the manufacture of a medicament for the treatment of infection due to *C.pneumoniae*.

Also provided according to the present invention is a method of manufacture of a medicament for the treatment of infection due to *C. pneumoniae*, characterised in the use of a protein, immungenic fragment or inhibitor according to the present invention.

Also provided according to the present invention is a method of treatment of infection due to *C. pneumoniae*, comprising the step of administering to a patient a medicament comprising a protein, immunogenic fragment or inhibitor according to the present invention. The exact dose of medicament administered to a patient may be readily determined using simple dose-response assays. Medicaments may additionally comprise a pharmaceutically acceptable carrier, diluent or excipient (Remington's Pharmaceutical Sciences and US Pharmacopeia, 1984, Mack Publishing Company, Easton, PA, USA)

It has not been previously suggested that that the protein of the present invention (or immunogenic fragments of same) is diagnostic for infection due to *C. pnemoniae*. Binding agents specific to the protein of the present invention (for example antibodies) may also be used diagnostically, for example in an ELISA-type test.

Thus also provided according to the present invention is the use of a protein, immunogenic fragment or binding agent according to the present invention in the manufacture of a diagnostic test for *C. pneumoniae*.

Also provided is a diagnostic test method for infection due to *C. pneumoniae* comprising the steps of:

i) reacting an antibody specific against the protein of the present invention with serum from a patient;

ii) detecting an antibody-antigen binding reaction; and

iii) correlating the detection of an antibody-antigen binding reaction with the presence of the protein.

Such test methods may also be performed using other binding agents specific to the protein of the present invention.

Also provided is a kit of parts for performing such a test, characterised in that it comprises antibody specific against the protein of the present invention.

The invention will be further apparent from the following description, with reference to the several figures of the accompanying drawings, which show, by way of example only, uses of the proteins of the present invention.

EXPERIMENTAL

Western Blotting - Using the Novex nuPAGE Eletrophoresis System.

1. SDS PAGE

Preparation of Sample:

1. 100 µl of Novex SDS Sample loading buffer was added to 400 µl of a preparation of a *Chlamydia pneumoniae* clinical isolate and the mixture placed into a boiling waterbath for 10 minutes.

2. 10µl of the mixture was loaded into each well of a Novex 4-12% Bis-Tris NuPage gel (1.0mm, 12 well). In addition, 4µl of Novex Multimark molecular weight standards were added to a single well on each gel.

3. Electrophoresis was performed using 1x Novex MOPS electrophoresis buffer at 200v for 40 minutes.

Western Transfer Protocol:

1. The blotting apparatus and the gel membrane "sandwiches" were assembled according to the protocol described in the Novex instruction booklet provided with the gels.

2. Blotting was performed using 1x Novex Transfer buffer containing 20% methanol. Transfer was carried out at 30v (constant) for 1 hour.

3. Following transfer, the membranes were removed from the apparatus and left to "Block" overnight in 3% Bovine Serum Albumin (BSA) at 4°C.

Probing With Patient's Serum:

1. The membranes were cut into strips and placed into the wells of incubation trays. Patients' serum was diluted 1 in 20 in 3% BSA and 2 mls added to each strip. (2 strips per patient).

2. The membranes were incubated at room temperature for 2 hours with agitation.

3. The strips were washed 5 times over 30 minutes with 0.85% NaCl/0.01% Tween 20.

4. 2 mls of goat anti-human IgM or IgG alkaline phosphatase conjugated anti-immunoglobulin diluted 1 in 4000 in 3% BSA were added to each strip. The strips were incubated for a further hour at room temperature with agitation.

5. The membranes were washed a further 5 times as previously described.

6. Antibody - antigen interation was visualised by addition NBT/BCIP (50mg/ml) in pH 9.5 phosphate buffer.

7. The reaction was allowed to proceed until the bands had reached the required intensity.

Sera

Group A: Children with respiratory tract infection and no evidence of Chlamydia pneumoniae as shown by negative microimmunofluorescence (less than 1 in 64) test (n=19).

Group B: Children with respiratory tract infection and a microimmunofluorescence titre greater than 1 in 512 (n=18).

Group C: Patients undergoing cardiac surgery for advance coronary disease (n=32). Ten of these had antibody on immunoblot.

Group D: Adults with respiratory tract infection and a chlamydia complement fixation test greater than 1 in 40 (n=27) using LGV 2 as an antigen.

Group E: Adults with pelvic inflammatory disease due to *Chlamydia trachomatis* (n=21).

Group F: Sera (n=11) which were positive for the 60/62 kDa doublet and band at 51 kDa were retested on antigen prepared from *Chlamydia pneumoniae* where the purified elementary bodies were incubated with 1% octylglucoside at 37°C for 30 minutes rather than in SDS.

Results:

Results of the sera blotting experiments are shown in Table 1. It should be noted that sera blotting determines the presence in patients of antibodies specific against a given antigen, and so when a patient has previously been infected by a pathogen and developed an immune response against an antigen, that immune response may still be detectable at a later date when the patient is no longer infected. Hence background results must be interpreted in light of the general infection of a population by the pathogen. For example,

the general population has an infection rate by adulthood of approximately 10% for *C. pneumoniae*, thus a background rate of detection of *C. pneumoniae* antigens of up to 10% should be expected.

Conclusions:

The sera from Group A children did not recognise *C.pneumoniae* on immunoblot. The Group B sera from children with evidence of *C.pneumoniae* infection recognised a range of antigens with apparent molecular weight ranging from 30 to 180 kDa. Of these for IgM an antigen complex at 60/62 kDa which occured as a doublet was immunodominant as well as an antigen at 51 kDa. For IgG the antibody was most pronounced for the antigen at 51 kDa. In the cardiac patients, 23 produced antibody and this was for IgM against the bands 67, 60/62 and 51 kDa. For IgG this was the band at 51 kDa. For Group D IgM was most pronounced for the 60/62 kDa doublet and IgG for the band at 180 kDa and the doublet at 60/62 kDa. This group of sera contain those with infection most likely due to *Chlamydia psittaci*. The sera from Group E patients infected with *Chlamydia trachomatis* did not cross-react.

Group F Sera

On reblotting with those sera previously positive for the 60/62 kDa doublet and 51 kDa, the doublet disappeared whilst the band at 51 kDa remained. This showed that the band at 51 kDa was stable to and released by octylglucoside treatment.

Solubility in Octyl Glucoside

Using samples from Group F patients, separation of antigens from elementary bodies using 1-D gel electrophoresis and SDS gave a different staining pattern compared to using 1-D gel electrophoresis and octyl glucoside. The 51 kDa band was still visible after octyl glucoside. The pair of antigenic bands at 60/62 kDa was not visible in octyl

glucoside. Therefore a distinguishing character of the 51 kDa antigen of the present invention is its solubility in octyl glucoside.

N-Terminal Amino Acid Sequencing

N-Terminal amino-acid sequencing was performed upon the 51 kDa band. The resulting sequence was then used to query the Chlamydia Genome Project database which identified the protein of SEQ ID NO: 2 and a *C. trachomatis* homologue.

Epitope Mapping

A series of overlapping nonapeptides covering the derived amino acid sequence of the protein were synthesised on polyethylene pins with reagents from an epitope scanning kit (Cambridge Research Biochemicals, Cambridge, UK) as described previously by Geysen *et al.* (1987, Journal of Immunological Methods, 102:259-274). Peptide 1 consisted of residues 1 to 9, peptide 2 consisted of residues 2 to 10 etc. The reactivity of each peptide with patient sera (diluted 1 in 2000) was determined for IgG by ELISA. Data were expressed as A405 after 30 min of incubation.

Results of the epitope mapping identified six epitopes displayed by the protein, having SEQ ID NOs: 3-11.

Indirect ELISA test with unbound peptides

Three areas (peptides having SEQ ID NOs: 9-11) were synthesised as short peptides by a BT7400 multiple peptide synthesiser (Biotech Instruments, Luton, UK). These were used in the indirect ELISA.

Patient sera from Groups A-E (above) (IgM and IgG) was used for the ELISA test.

By a simple adsorbtion of peptides to a microtitre plate the following procedure was performed for each peptide. The peptide was dissolved in 2 ml of 0.01 M phosphate buffer saline (PBS), pH 7.2 and diluted to a concentration of 10 µg/ml (1/100) in the same buffer.

(1) 150 µl aliquots of peptide (10 µg/ml in 0.01M PBS) were pipetted into the wells of a Falcon 3912 microassay plate and were incubated overnight at 4 °C.

(2) The unbound peptide was removed by washing four times (4 x 10 minutes) with 0.05% Tween 20 in 0.01 M PBS (pH 7.2).

(3) The plates were blocked with 2% skimmed milk-10% FCS in 0.01M PBS for 1 hour at 37 °C.

(4) The plates were washed four times (4 x 10 minutes) with 0.05% Tween 20 in 0.01M PBS and the serum under investigation was added (1/100 dilution in blocking solution) into the wells of micro assay plate (three wells used for each serum) and incubated for 2 hours at 37 °C.

(5) The plates were washed four times (4 x 10 minutes) with 0.05% Tween 20 in 0.01 M PBS and secondary antibody, anti-human IgM (or IgG) peroxidase conjugate (1/1000 dilution in blocking solution) was added and incubation proceeded for 1 hour at 37 °C.

(6) The plates were washed four times (4 x 10 minutes) with 0.05% Tween 20 in 0.01 M PBS, followed by a further washing with 0.01 M PBS. The plate was then incubated for 45 minutes at room temperature with agitation in 0.5 mg/ml of freshly prepared 2,2 Azino-bis [3-ethylbenz-thiazoline-6-sulfonic acid] diammonium (ABTS tablets) in pH 4.0 citrate buffer with 0.01% (w/v) hydrogen peroxide.

(7) Control wells were used in each plate. The three wells having ABTS solution only and three wells having ABTS solution plus anti-human IgG or IgM horseradish peroxidase conjugate only were used.

(8) Optical density (O.D.) measurements were made with an ELISA plate reader (Titertek Multiscan) at a wavelength of 405 nm.

(9) The average readings for each of three wells per patient's serum was determined. A positive result was taken to be an average OD of >0.4 for three wells.

Table 1

Apparent Molecular Weight (kDa)	Group B (N=18)		Group C (N=18)		Group D (N=27)		Group E (N=21)	
	IgM	IgG	IgM	IgG	IgM	IgG	IgM	IgG
180	1	2		2	1	6		1
130		2			1	4		
120	1	5		1	1	5		1
98		5		1	2	5		2
90		2				2		
67		2	5	1			1	1
60/62*	8	5	5		13	7	2	2
51	7	11	9	10	2	3	1	2
47	1	1	1		0	0	0	0
40	0	0	0	3	0	0	0	1
30		4	0	3		2		2

* runs as a doublet within 1 mm of each other

CLAIMS

1. A *C.pneumoniae* protein having the amino acid sequence of SEQ ID NO: 2 for use in a method of treatment or diagnosis of the human or animal body.

2. A nucleotide sequence encoding a protein according to claim 1 for use in a method of treatment of the human or animal body.

3. A nucleotide sequence according to claim 2, having the sequence of SEQ ID NO: 1.

4. The use of a protein, immunogenic fragment thereof or nucleotide sequence encoding same according to any one of the preceding claims in the manufacture if a medicament for the treatment of infection due to *C.pneumoniae*.

5. The use of an immunogenic fragment according to claim 4, having the amino acid sequence of any one of SEQ ID NOs: 3-11 in the manufacture of a medicament for the treatment of infection due to *C.pneumoniae*.

6. The use of an inhibitor specific against the protein, immunogenic fragment or nucleotide sequence encoding same according to any one of the preceding claims in a method of manufacture of a medicament for the treatment of infection due to *C.pneumoniae*.

7. The use of an inhibitor according to claim 6, the inhibitor being selected from the group of an antibody, DNA vaccine, ribozyme and antisense oligo nucleotide.

8. A method of manufacture of a medicament for the treatment of infection by *C.pneumoniae* characterised in the use of a protein, immunogenic fragment thereof or nucleotide sequence encoding same according to either one of claims 4 or 5.

9. A method of manufacture of a medicament for the treatment of infection due to *C.pneumoniae* characterised in the use of an inhibitor according to either one of claims 6 or 7.

10. The use of a protein according to claim 1 or an immunogenic fragment thereof or a binding agent specific to same or an inhibitor of same in the manufacture of a diagnostic test for *C.pneumoniae*.

11. A kit of parts for a diagnostic test for *C.pnemoniae*, characterised in that it comprises a protein according to claim 1 or an immunogenic fragment thereof or a binding agent specific to same or an inhibitor of same.

12. A diagnostic test method for infection due to *C.pneumoniae* comprising the steps of:

i) reacting an antibody specific against the protein according to claim 1 with serum from a patient;

ii) detecting an antibody - antigen binding reaction; and

iii) correlating the detection of an antibody - antigen binding reaction with the presence of the protein.

13. A diagnostic test method according to claim 12, being a method of diagnosis of the human or animal body.

14. A method of treatment of infection due to *C.pneumoniae* comprising the step of administering to a patient a medicament comprising a protein, immunogenic fragment thereof, nucleotide sequence encoding same or an inhibitor thereof according to any one of claims 4-7.

SEQUENCE LISTING

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gcc gca acc acg gta gca aca caa att aca gtt caa gct gtt gtc caa   960
Ala Ala Thr Thr Val Ala Thr Gln Ile Thr Val Gln Ala Val Val Gln
305                 310                 315                 320

gcg gtg aaa caa gct gtt atc aca gct gtc aga caa gcg atc acc gcg  1008
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Ala Val Lys Gln Ala Val Ile Thr Ala Val Arg Gln Ala Ile Thr Ala
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gct ata aaa gcg gct gtc aaa tct gga ata aaa gca ttt atc aaa act   1056
Ala Ile Lys Ala Ala Val Lys Ser Gly Ile Lys Ala Phe Ile Lys Thr
            340                 345                 350

tta gtc aaa gcg att gcc aaa gcc att tct aaa gga atc tct aag gtt   1104
Leu Val Lys Ala Ile Ala Lys Ala Ile Ser Lys Gly Ile Ser Lys Val
        355                 360                 365

ttc gct aag gga act caa atg att gcg aag aac ttc ccc aag ctc tcg   1152
Phe Ala Lys Gly Thr Gln Met Ile Ala Lys Asn Phe Pro Lys Leu Ser
    370                 375                 380

aaa gtc atc tcg tct ctt acc agt aaa tgg gtc acg gtt ggg gtt ggg   1200
Lys Val Ile Ser Ser Leu Thr Ser Lys Trp Val Thr Val Gly Val Gly
385                 390                 395                 400

gtt gta gtt gcg gcg cct gct ctc ggt aaa ggg att atg caa atg cag   1248
Val Val Val Ala Ala Pro Ala Leu Gly Lys Gly Ile Met Gln Met Gln
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ctc tcg gag atg caa caa aac gtc gct caa ttt cag aaa gaa gtc gga   1296
Leu Ser Glu Met Gln Gln Asn Val Ala Gln Phe Gln Lys Glu Val Gly
            420                 425                 430

aaa ctg cag gct gcg gct gat atg att tct atg ttc act caa ttt tgg   1344
Lys Leu Gln Ala Ala Ala Asp Met Ile Ser Met Phe Thr Gln Phe Trp
        435                 440                 445

caa cag gca agt aaa att gcc tca aaa caa aca ggc gag tct aat gaa   1392
Gln Gln Ala Ser Lys Ile Ala Ser Lys Gln Thr Gly Glu Ser Asn Glu
    450                 455                 460

atg act caa aaa gct acc aag ctg ggc gct caa atc ctt aaa gcg tat   1440
Met Thr Gln Lys Ala Thr Lys Leu Gly Ala Gln Ile Leu Lys Ala Tyr
465                 470                 475                 480

gcc gca atc agc gga gcc atc gct ggc gca cat aaa acc aat aat ttt   1488
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taa                                                              1491
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35 40 45

Gln Gly Lys Asn Thr Glu Met Glu Ser Asp Ala Thr Ile Ala Gly Ala
50 55 60

Ser Gly Lys Asp Lys Thr Ser Ser Thr Thr Lys Thr Glu Thr Ala Pro
65 70 75 80

Gln Gln Gly Val Ala Ala Gly Lys Glu Ser Ser Glu Ser Gln Lys Ala
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Gly Ala Asp Thr Gly Val Ser Gly Ala Ala Ala Thr Thr Ala Ser Asn
100 105 110

Thr Ala Thr Lys Ile Ala Met Gln Thr Ser Ile Glu Glu Ala Ser Lys
115 120 125

Ser Met Glu Ser Thr Leu Glu Ser Leu Gln Ser Leu Ser Ala Ala Gln
130 135 140

Met Lys Glu Val Glu Ala Val Val Val Ala Ala Leu Ser Gly Lys Ser
145 150 155 160

Ser Gly Ser Ala Lys Leu Glu Thr Pro Glu Leu Pro Lys Pro Gly Val
165 170 175

Thr Pro Arg Ser Glu Val Ile Glu Ile Gly Leu Ala Leu Ala Lys Ala
180 185 190

Ile Gln Thr Leu Gly Glu Ala Thr Lys Ser Ala Leu Ser Asn Tyr Ala
195 200 205

Ser Thr Gln Ala Gln Ala Asp Gln Thr Asn Lys Leu Gly Leu Glu Lys
210 215 220

Gln Ala Ile Lys Ile Asp Lys Glu Arg Glu Glu Tyr Gln Glu Met Lys
225 230 235 240

Ala Ala Glu Gln Lys Ser Lys Asp Leu Glu Gly Thr Met Asp Thr Val
245 250 255

Asn Thr Val Met Ile Ala Val Ser Val Ala Ile Thr Val Ile Ser Ile
260 265 270

Val Ala Ala Ile Phe Thr Cys Gly Ala Gly Leu Ala Gly Leu Ala Ala
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Gly Ala Ala Val Gly Ala Ala Ala Ala Gly Gly Ala Ala Gly Ala Ala
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Ala Ala Thr Thr Val Ala Thr Gln Ile Thr Val Gln Ala Val Val Gln
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Ala Val Lys Gln Ala Val Ile Thr Ala Val Arg Gln Ala Ile Thr Ala
325 330 335

Ala Ile Lys Ala Ala Val Lys Ser Gly Ile Lys Ala Phe Ile Lys Thr
340 345 350

Leu Val Lys Ala Ile Ala Lys Ala Ile Ser Lys Gly Ile Ser Lys Val
355 360 365

Phe Ala Lys Gly Thr Gln Met Ile Ala Lys Asn Phe Pro Lys Leu Ser
370 375 380

Lys Val Ile Ser Ser Leu Thr Ser Lys Trp Val Thr Val Gly Val Gly
385 390 395 400

Val Val Val Ala Ala Pro Ala Leu Gly Lys Gly Ile Met Gln Met Gln
405 410 415

Leu Ser Glu Met Gln Gln Asn Val Ala Gln Phe Gln Lys Glu Val Gly
420 425 430

Lys Leu Gln Ala Ala Ala Asp Met Ile Ser Met Phe Thr Gln Phe Trp
435 440 445

Gln Gln Ala Ser Lys Ile Ala Ser Lys Gln Thr Gly Glu Ser Asn Glu
450 455 460

Met Thr Gln Lys Ala Thr Lys Leu Gly Ala Gln Ile Leu Lys Ala Tyr
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